April 17, 2006

**Memorandum**

Subject: Toxicology Disciplinary Chapter for the Re-Registration Eligibility Decision (RED) Risk Assessment

Active Ingredient: Ortho-phenylphenol and salts
PC Codes 064103, 064104, 064108

DP Barcode:

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## 1.0 HAZARD CHARACTERIZATION

2-phenylphenol (OPP) is a white flaky crystal soluble only in alcohols or ethers. The potassium and sodium salts are soluble in water. Due to similarities between 2-phenylphenol and potassium and sodium salts, this report is a composite of toxicology of these chemicals is composited in this report. Currently, there are 124 active 2-phenylphenol and salts registered. Of these 124, seven are manufacturing use/ technical grade active ingredients (MUP/TGAI) products.

2-phenylphenol (OPP) is a bacteriostat, microbiostat, menaticide, fumigant, and bacteriocide chemical. As a fungicide, tolerances have been established (40 CFR 180.129) for combined residues of 2-phenylphenol and its sodium salt from postharvest application on apples, cantaloupes, carrots, cherries, citrus, cucumbers, grapefruits, kiwifruits, kumquats, lemons, limes, nectarines, oranges, bell peppers, peaches, pears, pineapples, plums and prunes, sweet potatoes, tangerines, and tomatoes. In addition, OPP is used in applications to hard surfaces (walls, floors, barns) and agricultural premises and equipment, wood preservation for control of sapstain and mold, food handling surfaces and equipment, air deodorization, commercial and institutional premises, medical premises, residential and public access premises (carpet, hard surfaces, crack and crevice treatment), material preservatives (stains and paints, metalworking fluids, textiles, paper slurries, cement mixtures, glues and adhesives, and consumer, household and institutional cleaning products).

The acute toxicity database for OPP and salts shows that by the oral route, a Toxicity Category III is assigned based on results of two submitted studies (MRIDs 43334201 and 43334204) showing oral $LD_{50}$ values of 2733 mg/kg (combined) and values of 846 and 591 mg/kg ( males and females respectively). By the dermal route, an $LD_{50}$ value of > 5000 mg/kg was obtained in a submitted study (MRID 00078779). In a submitted acute inhalation toxicity study (MRID 42333101), animals exposed nose-only to an aerosol of OPP (0.036 mg/L) showed no mortality; however, this study is currently not acceptable but could be upgraded if information is provided that an adequate (higher) atmospheric concentration of OPP could not be generated and that smaller particle sizes could not be achieved. A primary eye irritation study was conducted (MRID 00139884) but the study was considered unacceptable because the observation period employed in the study (7 days) was not long enough to assign a Toxicity Category. OPP and its sodium salt are severe (Toxicity Category I) dermal irritants. OPP and its sodium salt are not dermal sensitizers.

For subchronic toxicity, several studies from the open literature were provided, but only one oral (MRID 40760206) and one dermal study (MRID 42881901) are considered acceptable.

In a 90-day oral toxicity test (MRID 40760206), OPP (>98% purity) was administered in feed to 10 rats/sex/dose at concentrations of 0, 0.156, 0.313, 0.625, 1.25, or 2.5% (0, 182, 391, 761, 1669, or 2798 mg/kg/day and 0, 202, 411, 803, 1650, or 3014 mg/kg/day for males and females,

respectively) for 13 weeks. The subchronic toxicity NOAEL is 0.625 % (761 mg/kg/day, males; 803 mg/kg/day, females). The subchronic toxicity LOAEL is 1.25% (1669 mg/kg/day, males; 1650 mg/kg/day, females), based on significant reductions in body weight gain and food and water consumption.

In a 21-day dermal toxicity study (MRID 42881901), Fischer 344 rats (5/sex) were administered OPP (99.82% a.i.) for a total of 15 doses. Rats received doses of 0, 100, 500, or 1000 mg/kg/day for 6 hours per day. The highest dose tested, 1000 mg/kg/day, a limit dose for repeated dermal dosing regimens, produced no significant signs of systemic toxicity. Erythema and scaling were present in male and female rats at the 500 and 1000 mg/kg dose levels, with more severe irritation in the females. Microscopically, an increased incidence of acanthosis and hyperkeratosis was observed in male and female rats at the 500 and 1000 mg/kg dose levels. The systemic toxicity NOAEL is greater than or equal to 1000 mg/kg/day (highest dose tested), and the systemic toxicity LOAEL is greater than 1000 mg/kg/day (not established). The dermal toxicity NOAEL is 100 mg/kg/day based on an increased incidence of dermal irritation in male and female rats at the LOAEL of 500 mg/kg/day.

The database for developmental toxicity is considered complete with two studies. In one study (MRID 92154037, reformat of 00067616 and 00164362), OPP (99.69% a.i.) in cottonseed oil was administered, presumably via oral gavage, to mated female Sprague-Dawley rats (37, 27, 27, and 26/group, respectively) at dose levels of 0, 100, 300, or 700 mg/kg/day from gestation days (GD) 6 to 15, inclusive. Minimal maternal toxicity was noted in the mid-dose group (91% of control) and greater maternal toxicity was noted in the high-dose group (79% of control) during the dosing period as a decrease in body weight gain. No developmental toxicity was noted in the dose levels tested. In a second prenatal developmental toxicity study (MRID 41925001, 41925002, and 41925003), inseminated New Zealand White rabbits (7 females/group) were administered OPP (99.88% a.i.) on days 7-19 of presumed gestation by oral gavage at doses of 0, 25, 100, or 250 mg/kg/day. There were no statistically or biologically significant treatment-related differences in the incidence of fetal malformations or variations in any of the dose groups tested. Findings were sporadic, not dose-related and/or within the range of historical control data.

In a 2-generation reproductive toxicity study (MRID 43928801), OPP was administered to Sprague-Dawley rats, 30/sex/dose, in the diet at concentrations of 0, 20, 100, or 500 mg/kg/day. No treatment-related effects were observed on overall mortality, except for one $F_0$ male rat receiving 500 mg/kg/day that died due to kidney failure. Urinary bladder calculi observed grossly ($F_0$: 4/30 vs. 0/30 for controls, not significant; $F_1$: 7/30 vs. 0/30 for controls, $P<0.05$) and microscopically ($F_0$ and $F_1$: 4/30 vs. 0/30, not significant) at 500 mg/kg/day in adult males were considered treatment-related. Wet/stained ventrum observed in the $F_0$ and $F_1$ adult males (not significant) at 500 mg/kg/day considered treatment-related. Other microscopic lesions attributed to treatment of male rats with 500 mg/kg/day OPP included simple transitional cell hyperplasia ($F_0$ and $F_1$, $p<0.05$), nodular/ papillary transitional cell hyperplasia of the urinary bladder ($F_0$ and

$F_1$, $p<0.05$) and chronic inflammation in the urinary bladder ($F_0$ and $F_1$, $p<0.05$). The average severity ratings but not the incidences were significantly increased ($p<0.05$) for chronic inflammation in the kidney ($F_0$), debris in the renal pelvis ($F_1$), and dilation of the ureter ($F_0$). No treatment-related pathologic lesions were observed in adult females. No treatment-related effects on reproductive function or performance were observed in male or female rats of either generation. No treatment-related effects occurred on viability, clinical signs, litter size at birth, or at the end of lactation or sex ratio for the $F_1$ or $F_2$ pups. Body weights in 21-day old pups in the 500 mg/kg/day group were decreased significantly ($p<0.01$) in both litters of each generation. $F_{2b}$ pups at 500 mg/kg/day weighed 7% less ($p<0.05$) than controls on day 14 of lactation; no other statistically significant effects on pup weights were observed. Pup weight gain at 500 mg/kg/day was reduced by 12 to 14% over the entire lactation period. The reduced pup weights and weight gain is not attributed to lactational effects in the dams, but is considered to be related to consumption of the treated food. The LOAEL is 500 mg/kg/day in males and females, based on reduced body weight and body weight gain in the adults, reduced body weight in 21-day old pups, clinical signs in adult male rats, microscopic lesions in the kidneys, and gross and microscopic lesions in the urinary bladder of adult male rats, and the death of one adult male rat due to kidney failure. The corresponding NOAEL is 100 mg/kg/day. No treatment-related reproductive toxicity occurred in male or female rats; therefore the reproductive NOAEL is >500 mg/kg/day.

In a one year chronic toxicity study in dogs (MRID 41656401), OPP was administered by gavage to groups of male and female beagle dogs at doses of 0, 30, 100, or 300 mg/kg/day five days a week for 52 weeks. Systemic toxicity was observed at 300 mg/kg/day in the form of increased incidence of emesis and volume of emesis (supported by the results of a range-finding study where 200 and 400 mg/kg/day produced increased emesis). Weight gain was decreased in female dogs at the high dose (84% of control at study end). Food efficiency was also slightly decreased in high dose female dogs compared to control at 90 and 365 days. The systemic NOAEL was determined to be 100 mg/kg/day, based on clinical signs of toxicity, reduced body weight gain, and reduced food efficiency at 300 mg/kg/day.

In mutagenicity studies submitted to the Agency, OPP showed generally negative responses. Most of the submitted bacterial reverse mutation tests were negative, but one test (MRID# 470233020) showed a weakly positive response in one bacterial strain (TA1535) in the absence of metabolic activation, with 2.05 to 2.9 fold increases at OPP concentrations of 60-200 µg/plate. In an *in vitro* mammalian cell gene mutation test (MRID470233020) with 99% OPP, results were negative except for a dose-related general toxicity. An *In vitro* mammalian chromosome aberration test (470233020) was negative using 99% pure OPP. The study was conducted on Chinese hamster fibroblast cell line and Chinese hamster ovary cells.
A study on Unscheduled DNA synthesis in rat hepatocyte cultures was negative for all doses. Toxic effects were observed at the $1 \times 10^{-3}$ and $1 \times 10^{-2}$ M dose levels. However, the non-linearity of the responses observed suggests that the tumor response observed in this rat study with OPP is consistent with a threshold effects involving oxidative damage and direct DNA damaging effect.

An *in vitro* sister chromatid exchange assay (MRID 470233020) using 99% a.i. OPP showed a slight increase in sister chromatid exchanges without metabolic activation. At dose levels of 14.9, 20.0, and 29.9 µg/ml, OPP showed only a weak response in CHO cells in the absence of metabolic activation.

The available data show no significant neurotoxic effects from administration of the chemical in experimental animal studies.

The metabolism and pharmacokinetics of ortho-phenylphenol have been examined in studies from the peer reviewed scientific literature (Reitz et al., 1983; Bartels et al., 1998). An oral dose of ortho-phenylphenol can be directly conjugated with glucuronic acid or sulfate to form the glucuronide and sulfate conjugate or can be metabolized by cytochrome P-450 isozymes to form hydroxylated metabolites (phenylhydroquinone and 2,4 dihydroxybiphenyl) which are then in turn conjugated with glucuronic acid or sulfate. At doses below approximately 200 mg/kg, ortho-phenylphenol is found primarily in urine as the glucuronide and sulfate conjugates in both rats and mice. With increasing dose, however, the metabolic profile changes and this has been postulated to be related to the carcinogenic mode of action for ortho-phenylphenol. Briefly, biotransformation of OPP initially involves formation of phenolic metabolites (such as 2,4'-dihydroxyphenyl and phenylhydroquinone) in the liver through the action of cytochrome P-450 (demonstrated by Ozawa et al. [Xenobiotica 30(10), 1005-1017, 2000], by rat CYP2C11 and possibly CYP2E1, and human CYP1A2. OPP, phenylhydroquinone, and 2,4'-dihydroxybiphenyl can themselves undergo conjugation reactions through the action of either sulfotransferase or glucuronidation phase II reactions. Phenylhydroquinone can also be converted to phenyl-1,4-benzoquinone by a secondary peroxidase-mediated activation in the kidney and/or bladder involving the prostaglandin endoperoxide synthase (PHS) complex. The involvement of PHS has been suggested on the basis of data submitted to the Office of Pesticide Programs (D203250), where in vitro incubations were conducted with microsomal PHS from ram seminal vesicles using ortho-phenylphenol (OPP) or the metabolites phenylhydroquinone (PHQ) and 2-phenyl-1,4-benzoquinone (PBQ). This study demonstrated a role for PHS in conversion of PHQ to PBQ.

## 2.0 Toxicology Data Requirements

| Test | Technical | |
|---|---|---|
| | **Required** | **Satisfied** |
| 870.1100 Acute Oral Toxicity ..... | Y | Y |
| 870.1200 Acute Dermal Toxicity ..... | Y | Y |
| 870.1300 Acute Inhalation Toxicity ..... | Y | N |
| 870.2400 Primary Eye Irritation ..... | Y | N |

| Test | Technical | |
|---|---|---|
| | **Required** | **Satisfied** |
| 870.2500 Primary Dermal Irritation..... | Y | Y |
| 870.2600 Dermal Sensitization..... | Y | Y |
| 870.6100 Acute Delayed Neurotox. (Hen)..... | N | |
| 870.6200a ....Acute Neurotox. Screening Battery (Rat) | N | |
| 870.3100 Oral Subchronic (Rodent) ..... | Y | Y |
| 870.3150 Oral Subchronic (Non-Rodent) ..... | Y | Y |
| 870.3200 21-Day Dermal ..... | Y | Y |
| 870.3250 90-Day Dermal ..... | N | |
| 870.3465 90-Day Inhalation ..... | Held in reserve | |
| 870.3700aDevelopmental Toxicity (rodent) ..... | Y | Y |
| 870.3700bDevelopmental Toxicity( non-rodent)..... | Y | Y |
| 870.3800 Reproduction ..... | Y | Y |
| 870.4100aChronic Toxicity (Rodent)..... | Y | Y |
| 870.4100bChronic Toxicity (Non-rodent) ..... | Y | Y |
| 870.4200aOncogenicity (Rat) ..... | Y | Y |
| 870.4200bOncogenicity (Mouse) ..... | Y | Y |
| 870.4300 Chronic/Oncogenicity ..... | Y | Y |
| 870.5100 MutagenicityGene Mutation - bacterial..... | Y | Y |
| 870.5300 MutagenicityGene Mutation - mammalian ... | Y | |
| 870.5395 MutagenicityMammalian erythrocyte micronucleus | Y<br>N | Y<br>N |
| 870.6100 90-Day Neurotoxicity (hen) ..... | N | -- |
| 870.6200b90 Day Neuro. Screening Battery (Rat)..... | N | -- |
| 870.6300 Develop. Neuro..... | N | -- |
| 870.7485 General Metabolism..... | Y | Y |
| 870.7600 Dermal Penetration ..... | Y | Y |

## 3.0 DATA GAPS

The acute inhalation toxicity study might be upgraded if additional information is provided on generation of the test atmosphere as indicated in the review. The primary eye irritation study should be repeated as the observation period post-dosing (7 days) was not long enough to establish a Toxicity Category. A repeat dose inhalation toxicity study is held in reserve pending the outcome of the preliminary risk assessment.

## 4.0 HAZARD ASSESSMENT

### 4.1 Acute Toxicity

The acute toxicity database for OPP and salts shows that by the oral route, a Toxicity Category III is assigned based on results of two submitted studies (MRIDs 43334201 and 43334204) showing oral $LD_{50}$ values of 2733 mg/kg (combined) and values of 846 and 591 mg/kg ( males and females respectively). By the dermal route, an $LD_{50}$ value of > 5000 mg/kg was obtained in a submitted study (MRID 00078779). In a submitted acute inhalation toxicity study (MRID 42333101), animals exposed nose-only to an aerosol of OPP (0.036 mg/L) showed no mortality; however, this study is currently not acceptable but could be upgraded if information is provided that an adequate (higher) atmospheric concentration of OPP could not be generated and that smaller particle sizes could not be achieved. A primary eye irritation study was conducted (MRID 00139884) but the study was considered unacceptable because the observation period employed in the study (7 days) was not long enough to assign a Toxicity Category. OPP and its sodium salt are severe (Toxicity Category I) dermal irritants. OPP and its sodium salt are not dermal sensitizers.

Adequacy of database for Acute Toxicity:

**Table 1. Acute Toxicity Profile for OPP and Salts**

| Guideline Number | Study Type/Test substance (% a.i.) | MRID Number/ Citation | Results | Toxicity Category |
|---|---|---|---|---|
| 870.1100 (§81-1) | Acute Oral- Rat OPP purity 99.9% | 43334201 | $LD_{50}$ = 2733 mg/kg | III |
| 870.1100 (§81-1) | Acute Oral- Rat OPP, sodium salt purity 99.1% | 43334204 | $LD_{50}$ = 846 mg/kg (male) $LD_{50}$ = 591 mg/kg (female) | III |
| 870.1200 (§81-2) | Acute Dermal- Rat OPP 99.73% a.i. | 00078779 | $LD_{50}$ > 5000 mg/kg | IV |
| 870.1300 (§81-3) | Acute Inhalation – Rat OPP 99.9% a.i. | 42333101 | Unacceptable study | NA |
| 870.2400 (§81-4) | Primary Eye Irritation – Rabbit Dowicide® 1 | 00139884 | Unacceptable study | NA |
| 870.2500 (§81-5) | Primary Dermal Irritation- Rabbit OPP purity 99.9% | 43334202 | Primary Irritant | I |

| Table 1. Acute Toxicity Profile for OPP and Salts | | | | |
|---|---|---|---|---|
| **Guideline Number** | **Study Type/Test substance (% a.i.)** | **MRID Number/ Citation** | **Results** | **Toxicity Category** |
| 870.2600 (§81-6) | Dermal Sensitization - Guinea pig OPP purity 99.9% | 43334203 | Not a sensitizer. | No |
| 870.2600 (§81-6) | Dermal Sensitization - Guinea pig OPP, sodium salt purity 99.1% | 43334205 | Not a sensitizer. | No |

### 4.2 Subchronic Toxicity

Adequacy of database for Subchronic Toxicity: For subchronic toxicity, several studies from the open literature were provided, but only one oral and one dermal study are considered acceptable (MRID 40760206 and 42881901, respectively).

**870.3100 90-day Oral Toxicity – Rats**

In a 90-day oral toxicity test (MRID 40760206) designed to determine the subchronic toxicity effects of repeated dietary exposure to OPP (>98% purity) in F344/DuCrj rats. OPP was administered in feed to 10 rats/sex/dose at concentrations of 0, 0.156, 0.313, 0.625, 1.25, or 2.5% (0, 182, 391, 761, 1669, or 2798 mg/kg/day and 0, 202, 411, 803, 1650, or 3014 mg/kg/day for males and females, respectively) for 13 weeks. Animals were observed twice daily for changes in body weight and food and water consumption.

Mortality occurred in treated animals within 2 weeks of initiating the study, with death in 20% of males (4 days into study) and 10% of females (8 days into study) in the 2.5% dose group. Food consumption was slightly decreased in males and females of the 1.25% dose group. Males administered 2.5% OPP exhibited significant decreases from control in food intake. The discrepancy in food intake was greatest in the first week but decreased as the study progressed. Females of this group also exhibited a reduction in food consumption that was significantly less than the control until week 8; however, the decreased food intake trend continued throughout the remainder of the study. Additionally, the 2.5% rats spilled an excessive amount of feed at the initial stage of the study and they tended to be thin throughout the study period.

There were no other effects on food consumption in animals of the other dose levels except for males treated with 0.313% OPP. These rats showed significant increases in food consumption and food intake/body weight that appeared to be reflected in the body weight changes. Overall the feeding efficiency (increase in body weight over unit time in grams/feed intake in grams) was slightly lower in groups fed on feed containing high OPP concentrations.

Water consumption was significantly decreased from controls in the first week of the study in the 1.25 and 2.5% dose groups. There were no significant changes from controls in body weight gain in animals treated with OPP concentrations equal to or less than 0.625%. Weight gain was inhibited in males and females of the 1.25% dose group, with maximum inhibition ratios of 14 and 7%, respectively. The significant weight loss of 1.25% females occurred in the first 8 weeks of the study. Body weight gain was significantly reduced from controls in both male and female rats in the 2.5% OPP dose group.

The hemoglobin (Hgb) and mean red blood corpuscle hemoglobin concentration (MCHC) were significantly lower than controls in 1.25 and 2.5% females, while hematological analyses in the 2.5% males showed significant decreases from controls in red blood corpuscles (RBC), Hgb, and MCHC. There was a slight tendency for animals to be anemic in groups fed higher dosages of OPP. No treatment-related effects were observed in the serum analyses. Pathological and histological observations indicated treatment-related inflammation of the kidneys in both male and female rats (most pronounced in the 2.5% group) and abnormal growth in the mucous membrane of the male bladder (most pronounced in the 1.25% group).

**The subchronic toxicity NOAEL is 0.625% (761 mg/kg/day, males; 803 mg/kg/day, females). The subchronic toxicity LOAEL is 1.25% (1669 mg/kg/day, males; 1650 mg/kg/day, females), based on significant reductions in body weight gain and food and water consumption.**

This study is classified as **Acceptable - Guideline.**

**870.3200 21-Day Dermal Toxicity Study – Rat**

In a 21-day dermal toxicity study (MRID 42881901) of systemic toxicity in Fischer 344 rats, male and female (5/sex/dose) were administered OPP (99.82% a.i.) over a 21 day study period for a total of 15 doses of 0, 100, 500, or 1000 mg/kg/day for 6 hours per day.

The highest dose tested, 1000 mg/kg/day, a limit dose for repeated dermal dosing regimens, produced no significant signs of systemic toxicity. Erythema and scaling was present in male and female rats at the 500 and 1000 mg/kg dose levels, with more severe irritation effects observed in the females. Microscopically, an increased incidence of acanthosis and hyperkeratosis was observed in male and female rats at the 500 and 1000 mg/kg dose levels.

**The systemic toxicity NOAEL is greater than or equal to 1000 mg/kg/day (highest dose tested), and the systemic toxicity LOAEL is greater than 1000 mg/kg/day (not established). The dermal toxicity NOAEL is 100 mg/kg/day based on an increased incidence of dermal irritation reactions in male and female rats observed at the LOAEL of 500 mg/kg/day.**

**This study is classified as Acceptable-Guideline.**

### 4.3 Prenatal Developmental Toxicity

Adequacy of database for Prenatal Developmental Toxicity: The database for developmental toxicity is considered complete with two acceptable guideline studies, one in the rat (MRID 92154037, reformat of 00067616 and 00164362) and another in the rabbit (MRID 41925001, 41925002, and 41925003).

### 870.3700 Prenatal Developmental Toxicity– Rat

In a prenatal developmental toxicity study (MRID 92154037, reformat of 00067616 and 00164362), OPP (purity 99.69%) in cottonseed oil, was administered presumably by oral gavage (not specified) to groups of 37, 27, 27, and 26 rats/dose by gavage at dose levels of 0, 100, 300, or 700 mg/kg/day, respectively, from gestation days (GD) 6 to 15, inclusive. The animals were checked daily from gestation day 6 for indications of toxicity. Body weights were recorded daily from gestation days 6 through 15 and on gestation days 16 and 21. Food and water consumption were measured at 3 day intervals beginning on gestation day 6. Examinations at sacrifice consisted of a determination of the number and position of live, dead, and resorbed fetuses and staining of apparent nonpregnant uteri along with liver weights.

Minimal maternal toxicity was noted in the mid-dose group (91% of control) and greater maternal toxicity was noted in the high dose group (79% of control) during the dosing period as a decrease in body weight gain. Food consumption and food efficiency were slightly reduced in the mid and high dose groups during the dosing period. Also, the high dose group had reduced liver weights. **The maternal toxicity NOAEL is 100 mg/kg/day based on decreased body weight gains, food consumption and food efficiency. The maternal toxicity LOAEL is 300 mg/kg/day.**

No developmental toxicity was noted at the dose levels tested. **The developmental toxicity NOAEL is greater than or equal to 700 mg/kg/day (highest dose tested). The developmental toxicity LOAEL is greater than 700 mg/kg/day (not established).**

This study is classified as **Acceptable - Guideline**.

### 870.3700 Prenatal Developmental Toxicity – Rabbit

In a prenatal developmental toxicity study in rabbits (MRID 41925001, 41925002, and 41925003), inseminated New Zealand White rabbits (7 females/group) were administered OPP (99.88% a.i.) on days 7-19 of presumed gestation by oral gavage at doses of 0, 25, 100, or 250 mg/kg/day. All animals were observed daily for signs of toxicity during the course of the study with body weights recorded on gestation days 0, 20, and 28 and then daily during the dosing

period. Any animal that died or was sacrificed on study and all surviving animals at study termination were subjected to complete necropsy. Fetuses were examined for external, visceral, and skeletal alterations.

Administration of ortho-phenylphenol produced evidence of systemic toxicity at the 100 mg/kg/day (mid-dose) and 250 mg/kg/day (high-dose) levels. An increase in mortality occurred at the highest dose tested (three dams compared to one dam in the control group). Treatment-related alterations in microscopic kidney structure, primarily consisting of inflammation and tubular degeneration, were noted only in the high-dose animals. Although observations of blood in the feces, urine, or cage pan was noted in the mid-dose (three dams compared to one control dam) and high-dose (6 dams compared to one control dam) groups, these effects were determined to be of no toxicological significance because there was no correlation of these effects with signs of abortion and/or gross/microscopic pathologies. **The maternal toxicity NOAEL is 100 mg/kg/day and the maternal toxicity LOAEL is 250 mg/kg/day based upon increased incidence of mortality and renal inflammation/tubular degeneration.**

There were no statistically or biologically significant treatment-related differences in the incidence of fetal malformations or variations in any of the dose groups tested. Findings were sporadic, not dose-related and/or within the range of historical control data. **Therefore, the developmental toxicity NOAEL is greater than or equal to 250 mg/kg/day (highest dose tested) and the developmental LOAEL is greater than 250 mg/kg/day (not established).**

This study is classified as **Acceptable - Guideline**.

### 4.4 Reproductive Toxicity

Adequacy of database for Reproductive Toxicity: There was one acceptable/guideline 2-generation reproductive toxicity study (MRID 43928801). OPP was administered to groups of 30 male and 30 female Sprague-Dawley rats in the diet at concentrations delivering doses of 0, 20, 100, or 500 mg/kg/day.

### 870.3800 Reproduction and Fertility Effects – Rat

In a two-generation reproduction study (MRID 43928801) OPP (99+% a.i., Lot # PW08118LW) was administered to groups of 30 male and 30 female Sprague-Dawley rats in the diet at concentrations delivering doses of 0, 20, 100, or 500 mg/kg/day. Each group was administered the control or test diets continuously for 10 weeks prior to mating, during mating, gestation, and lactation through the production of two litters ($F_{1a}$, $F_{1b}$, $F_{2a}$, and $F_{2b}$) including a 14- or 20-day rest period after the first litters were weaned. The $F_1$ parents were selected when the pups were 21 days of age; the pups were weaned onto the same diets as received by their parents. The dietary concentrations were adjusted weekly based on the food consumption and body weight of the previous week to maintain a constant dose (mg/kg/day) except during gestation, lactation,

and from weaning through week 3 of the premating period for $F_1$ pups. During these times, the animals received the same dietary concentrations of test material as the respective groups during the last week of the $F_0$ premating period.

No treatment-related effects were observed in male or female adult rats administered OPP at concentrations of 20 or 100 mg/kg/day. No treatment-related effects were observed on overall mortality, except for one $F_0$ male rat receiving 500 mg/kg/day that died due to kidney failure. The only treatment-related clinical sign of toxicity was urine staining in 5/30 ($p<0.05$) $F_0$ and 8/30 ($p=0.01$) $F_1$ males given 500 mg/kg/day compared with 0/30 for each control group. A 500 mg/kg/day, body weights at the end of the 70-day premating period were decreased by 2% (not significant) in $F_0$ males, 7% ($p<0.01$) in $F_0$ females, 11% ($p<0.01$) in $F_1$ males, and 9% ($p<0.01$) in $F_1$ females. At the end of the study (day 175), body weights were decreased by 5% (not significant) in the $F_0$ males and by 11% ($p<0.01$) in $F_1$ males administered 500 mg/kg/day. Corresponding reductions in weight gain during the 70-day premating period were -9 and -10% for $F_0$ and $F_1$ males and -19 and -8% for $F_0$ and $F_1$ females at 500 mg/kg/day compared with weight gain in the controls. Reductions in weight gain after 175 days of treatment were -19 and -10% in the $F_0$ and $F_1$ males. In contrast to weight gain, food consumption by males and females of both parental generations administered 500 mg/kg/day generally exceeded that of controls, and the $F_1$ dams weighed 6 to 8% less ($P<0.05$ or $<0.01$) than controls and the $F_1$ dams weighed 5% to 8% less (not significant, $p<0.05$ or $p<0.01$) than controls. Weight gain in 500 mg/kg/day group dams during gestation was similar to that of controls ranging from +1 to -7% of the control value for both parental generations; during lactation, weight gain for all treated groups in both generation ranged from -57 to +288% and showed no clear dose-related trends. For the first 124 days of lactation, food consumption in dams receiving 500 mg/kg/day ranged from 103 to 112% of the control values.

Urinary bladder calculi observed grossly ($F_0$: 4/30 vs. 0/30 for controls, not significant; $F_1$: 7/30 vs. 0/30 for controls, $P<0.05$) and microscopically ($F_0$ and $F_1$: 4/30 vs. 0/30, not significant) at 500 mg/kg/day in adult males were considered to be related to treatment with the test material. Wet/stained ventrum observed ($F_0$: 2/30 vs. 0/30 for control, not significant; $F_1$: 5/30 vs. 0/30 for controls, not significant) at 500 mg/kg/day in adult males was considered to be treatment-related. Other microscopic lesions attributed to treatment of male rats with 500 mg/kg/day of the test material included simple transitional cell hyperplasia ($F_0$: 22/30 vs. 1/30; $F_1$: 27/30 vs. 0/30; $p<0.05$), nodular/ papillary transitional cell hyperplasia of the urinary bladder ($F_0$: 16/30 vs. 1/30; $F_1$: 19/30 vs. 0/30; $p<0.05$) and chronic inflammation in the urinary bladder ($F_0$: 13/30 vs. 0/30; $F_1$: 12/30 vs. 0/30; $p<0.05$). The average severity ratings but not the incidences were significantly increased ($p<0.05$) for chronic inflammation in the kidney [$F_0$: 4/30 (2.8) vs. 0/30] debris in the renal pelvis [$F_1$: 4/30 (2.5) vs. 0/30], and dilation of the ureter [$F_0$: 4/30 (1.8) vs. 0/30]. No treatment-related pathologic lesions were observed in adult females.

No treatment-related effects on reproductive function or performance were observed in male or female rats of either generation. No treatment-related effects occurred on viability, clinical

signs, litter size at birth, or at the end of lactation or sex ratio for the $F_1$ or $F_2$ pups. Body weights in 21-day old pups in the 500 mg/kg/day group were decreased significantly ($p<0.01$) in both litters of each generation (-10 to -12%). $F_{2b}$ pups at 500 mg/kg/day weighed 7% less ($p<0.05$) than controls on day 14 of lactation; no other statistically significant effects on pup weights were observed. Pup weight gain at 500 mg/kg/day was reduced by 12 to 14% over the entire lactation period. The reduced pup weights and weight gain is not attributed to lactational effects in the dams, but is considered to be related to consumption of the treated food.

**The parental toxicity LOAEL is 500 mg/kg/day in males and females, based on reduced body weight and body weight gain in the adults, reduced body weight in 21-day old pups, clinical signs in adult male rats, microscopic lesions in the kidneys, and gross and microscopic lesions in the urinary bladder of adult male rats, and the death of one adult male rat due to kidney failure. The parental toxicity NOAEL is 100 mg/kg/day. No treatment-related reproductive toxicity occurred in male or female rats; therefore the reproductive NOAEL is >500 mg/kg/day.**

This study is classified as **Acceptable - Guideline**.

### 4.5 Chronic Toxicity

Adequacy of database for Chronic Toxicity: The database is considered adequate for chronic toxicity of OPP.

### 870.4300 Combined chronic toxicity / Carcinogenicity – Rat

In a combined chronic toxicity /carcinogenicity study (MRID 43954301) CDF rats from SASCO, Inc., Madison WI received OPP (99.5—100% a.i.; Batch # S-01-93, Mixture of Bayer AG, Leverkusen, Germany and Dow, Midland, Michigan) in the diet for 24 months at dose levels of 0, 800, 4000 and 8000 ppm in males, and 0, 800, 4000, and 10000 ppm in females (39, 200, and 402 mg/kg/day for males for the 800, 4000, and 8000 ppm dose groups and 49, 248, and 647 mg/kg/day for females fat: the 800, 4000, and 10000 ppm dose groups). Interim sacrifice groups of twenty animals/sex for control and high dose groups and ten animals/sex for low and mid dose groups were sacrificed at 12 months. Systemic toxicity was noted as decreased body weights ($p < 0.05$) and body weight gains in both males and females of the mid and high dose groups during the first 13 weeks of- the study (for the 2-year carcinogenicity group). At study termination, only the high dose groups had reduced body weights ($p < 0.05$) and body weight gains. Food consumption was slightly decreased in the 2- year carcinogenicity group in the high dose group at all time points measured and was decreased in the mid dose females at 13 weeks. Food efficiency determined for the first 13 weeks was slightly decreased in the mid dose group and greatly decreased in the high dose, group. There was an increase in observed masses in the

urinary bladder of high dose males at 24 months. High dose females had an increased incidence of kidneys with pitted zones at 24 months. Mid and high dose females had an increase in wet/stained ventrum at 12 months and both high dose males and females had a similar observation at 24 months, this was attributed to the urine and red staining in the perigenital area noted in the clinical observation data. Non-neoplastic observations noted an increase in incidence of calculus in the kidneys in high dose males at the 12 month sacrifice and the 24 month study termination. There was also increased hyperplasia of the urinary bladder at 12 and 24 months in high dose males (and high dose females at 24 months) along with an increase in congestion, hemorrhage, mineralization and necrosis of the urinary bladder at 24 months in high dose males. High dose males and females also had an increase in cysts of the kidney at 24 months. High dose females had an increase in hyperplasia of the kidney along with increased infarct, acute inflammation and mineralization of the kidney. **Based on the results of this study, the Systemic Toxicity NOEL is equal to 800 ppm (39 mg/kg/day for males and 49 mg/kg/day for females and the Systemic Toxicity LOEL is equal to 4000 ppm (200 mg/kg/day for males and 248 mg/kg/day for females) based on decreased body weight gains, decreased food consumption and reduced food efficiency, and increased clinical and gross pathological signs of toxicity.**

This study is classified as **Acceptable – Guideline**.

In a carcinogenicity study (MRID# 43545501) B6C3F1 albino mice (50/sex/dose group) from Charles River Laboratory, Portage, MI received ortho-phenylphenol (99.88% a.i.; Lot# 8800005-24, mixture of Dow Chemical Company and Miles, Inc. products) in the diet for 24 months at dose levels of 0 250, 500 and 1000 Mg/kg/day. A satellite group of ten animals/sex/dose group were sacrificed at 12 months.

Systemic toxicity was noted in treated females at 3 months as decreased body weight gain (10-12%), statistically significant but not dose related. At 12 and 24 months there was a 14-25% decrease in body weight gain in males and females of the mid dose and a 27-38% decrease in the high dose groups. Treated females had a slightly reduced food consumption during the first 90 days. Food efficiency for this period was slightly reduced for the male dose groups and variable for the female dosed groups (no dose response effect). At 1 year there was no treatment related effects on food consumption and at 2 years there was a slight increase in food consumption in all treated groups. There was an increase in absolute and relative liver weights at 12 and 24 months in all treated males and females; also, treated males had increased adrenal absolute and relative weights at 24 months. Spleen weights (absolute and relative) in the males and females were reduced in all treated groups. **The Systemic Toxicity LOEL is less than or equal to 250 mg/kg/day and the Systemic Toxicity NOEL lees than 250 mg/kg/day based on increased liver and reduced spleen weights and gross observations in the liver of all treated animals**

This study is classified as Core-Minimum data and satisfies the guideline requirement (83-2b) for a carcinogenicity study in the mouse.

## 4.6 Carcinogenicity

Adequacy of database for Carcinogenicity: The database for carcinogenicity of OPP is considered adequate.

### 870.4300 Chronic Toxicity/Carcinogenicity Study – Rat

In a combined chronic toxicity/carcinogenicity study (MRID 43954301) CDF rats from SASCO, Inc., Madison, WI received ortho-phenylphenol, Technical Grade (99.5-100% a.i.; Batch #S-01-93, Mixture of Bayer AG, Leverkusen, Germany and Dow, Midland, Michigan) in the diet for 24 months at dose levels of 0, 800, 4000 and 8000 ppm in males (39, 200, and 402 mg/kg/day, respectively) and 0, 800, 4000, and 10000 ppm in females (49, 248, and 647 mg/kg/day, respectively). An interim sacrifice group of twenty animals/sex for control and high dose groups and ten animals/sex for the low and mid dose groups were sacrificed at 12 months.

Male rats had significant increasing trends, and significant differences in the pair-wise comparisons of the 8000 ppm dose group with the controls, for urinary bladder papillomas, transitional cell carcinomas, and papillomas and/or transitional cell carcinomas combined, all at $p < 0.01$ (Table 2). The statistical analyses of the male rats were based upon Peto's Prevalence Test (L. Brunsman, 5/19/05, TXR No. 0053394). There were no compound-related increases in tumors in female rats

### 870.4200 Carcinogenicity – Mouse

In a carcinogenicity study (MRID# 43545501) B6C3F1 albino mice (50/sex/dose group) from Charles River Laboratory, Portage, MI received ortho-phenylphenol (99.88% a.i.; Lot# 8800005-24, mixture of Dow Chemical Company and Miles, Inc. products) in the diet for 24 months at dose levels of 0 250, 500 and 1000 Mg/kg/day. A satellite group of ten animals/sex/dose group were sacrificed at 12 months.

Male mice had significant increasing trends, and significant differences in the pair-wise comparisons of the 1000 mg/kg/day dose group with the controls, for liver adenomas and adenomas and/or carcinomas combined, all at $p<0.01$ (L. Brunsman, 5/19/05, TXR No. 0053394). There was also a significant difference in the pair-wise comparison of the 500 mg/kg/day dose group with the controls for liver adenomas and/or carcinomas combined, at $p < 0.05$. Female mice had a significant difference in the pair-wise comparison of the 250 ppm dose group with the controls for liver carcinomas at $p< 0.05$. There were no other statistically significant findings for female mice (L. Brunsman, 5/19/05, TXR No. 0053394).

This study is classified as **Core-Minimum**.

### 4.7 Mutagenicity

An analysis of the genetic toxicology data from over 130 studies with OPP was undertaken by Brusick (2005) who found that there was no indication of gene mutations in bacteria or in mammalian cells such as Chinese hamster ovary (CHO) cells and that positive results with mouse lymphoma ($Tk^{+/-}$) were generally associated with cytotoxicity. Similarly, clastogenicity, which was the most frequently observed type of genotoxicity, was consistently linked with cytotoxicity. For OPP, the most common type of structural chromosome damage was chromosome breaks, an event that Brusick describes as typically resulting in cell death. Mixed results were found in studies assessing direct interaction with DNA damage. Based on the weight-of -the-evidence analysis, it was concluded that positive findings in genetic toxicology tests were related to 'excessive cytotoxicity, not direct DNA damage". Furthermore, Brusick (2005) states that agents that shift the normal cellular antioxidative balance and induce cytotoxicity are considered threshold-dependent because exposure levels that do not produce alterations in homeostais do not produce DNA damage (i.e., genotoxicity). In other words, oxidative damage, eventually leading to cell lethality, only occurs at concentrations that have exceeded the levels that can be handled by normal homeostasis. This observation is supported by the analysis of the carcinogenic mechanism of 2-phenylphenate by Niho et al. (2002). From the dose- and time-response studies with OPP and urinary bladder carcinogenicity in rats, investigators found that the tumor induction was a high-dose phenomenon, producing a steep dose response at 15,000 and 20,000 ppm but negative at 10,000 ppm. Similarly, a steep time response curve was plotted with transitional cell carcinoma development only seen in 4% of the animals after 24 weeks of continuous oral exposure but increasing dramatically after 24 (53%) and 52 (71%) weeks. The non-linearity of this response suggested to the authors that the tumor response observed in these studies with OPP is consistent with a threshold effect.

### 4.8 Neurotoxicity

Adequacy of database for Neurotoxicity: Although there are no studies conducted specifically addressing neurotoxicity of OPP, the available data suggest no significant neurotoxic effects of OPP in experimental animals.

### 4.9 Metabolism and Pharmacokinetics

Adequacy of database for Metabolism and Pharmacokinetics:

The metabolism and pharmacokinetics of ortho-phenylphenol have been examined in studies from the peer reviewed scientific literature (Reitz et al., 1983; Bartels et al., 1998). An oral dose of ortho-phenylphenol can be directly conjugated with glucuronic acid or sulfate to form the glucuronide and sulfate conjugate or can be metabolized by cytochrome P-450 isozymes to form hydroxylated metabolites (phenylhydroquinone and 2,4 dihydroxybiphenyl) which are then in

turn conjugated with glucuronic acid or sulfate. At doses below approximately 200 mg/kg, ortho-phenylphenol is found primarily in urine as the glucuronide and sulfate conjugates in both rats and mice. With increasing dose, however, the metabolic profile changes and this has been postulated to be related to the carcinogenic mode of action for ortho-phenylphenol. Briefly, Biotransformation of OPP initially involves formation of phenolic metabolites (such as 2,4'-dihydroxyphenyl and phenylhydroquinone) in the liver through the action of cytochrome P-450 (demonstrated by Ozawa et al. [Xenobiotica 30(10), 1005-1017, 2000], by rat CYP2C11 and possibly CYP2E1, and human CYP1A2. OPP, phenylhydroquinone, and 2,4'-dihydroxybiphenyl can themselves undergo conjugation reactions through the action of either sulfotransferase or glucuronidation phase II reactions. Phenylhydroquinone can also be converted to phenyl-1,4-benzoquinone by a secondary peroxidase-mediated activation in the kidney and/or bladder involving the prostaglandin endoperoxide synthase (PHS) complex. The involvement of PHS has been suggested on the basis of data submitted to the Office of Pesticide Programs (D203250), where in vitro incubations were conducted with microsomal PHS from ram seminal vesicles using ortho-phenylphenol (OPP) or the metabolites phenylhydroquinone (PHQ) and 2-phenyl-1,4-benzoquinone (PBQ). This study demonstrated a role for PHS in conversion of PHQ to PBQ.

The presence of PHS in the bladder epithelium has been proposed by Kolachana et al. (Carcinogenesis 12(1): 145-149, 1991) as possibly responsible for the activation of phenylhydroquinone to reactive intermediates in the bladder and kidney**.** The generation of PBQ is considered dose-dependent, appearing in increased quantity only at higher (>200 mg/kg/day) doses of OPP. The shift in biotransformation products with increased dose of OPP has been postulated to be associated with the non-linear response observed in tumorigenicity of the urinary bladder and liver, involving oxidative damage to cells and subsequent regenerative hyperplasia. With continued exposure, this process leads to development of tumors.

## 5.0 TOXICITY ENDPOINT SELECTION

### 5.1 See Section 7.1, Summary of Toxicological Doses and Endpoint Selection, Table 2.

### 5.2 Dermal Absorption

Dermal Absorption Factor: There are no available animal studies on the magnitude of dermal absorption of ortho-phenylphenol. One study (Timchalk et al., 1996) reported a dermal absorption value of 43% after application to the forearm of six human volunteers. However, there are currently significant scientific and political issues with respect to the Agency utilizing results from human studies for conduct of risk assessments. Therefore, the default value of 100% must be used for dermal absorption until such time that an acceptable dermal absorption study in animals is available or issues with respect to use of results from human studies are resolved.

### 5.3 Classification of Carcinogenic Potential

In accordance with the EPA Final Guidelines for Carcinogen Risk Assessment (March 29, 2005), the CARC classified OPP as "Not Likely to be Carcinogenic to Humans" based on convincing evidence that a non-linear mode of action for bladder tumors was established in rats. High doses of OPP lead to saturation of phase II detoxification enzyme pathways, resulting in increased amounts of the oxidative metabolites PHQ and/or PBQ. The generation of PBQ is considered dose-dependent, appearing in increased quantity only at higher doses of OPP (>200 mg/kg/day). The shift in biotransformation products with increased dose of OPP has been postulated to be associated with the non-linear response observed in tumorigenicity of the urinary bladder, involving oxidative damage to cells and subsequent regenerative hyperplasia. With continued exposure, this process leads to development of tumors. Evidence suggests that there are not sufficient oxidative metabolites generated in vivo to result in a genotoxic mode of action, but that a non-genotoxic mode of action is operative.

Although there is some mode of action data for the mouse liver tumors, the nature of these tumors and their response (benign tumors in one sex at the limit dose and one-half the limit dose in a susceptible strain) would not be the basis for quantification of human risk. However, data do suggest that this tumor type may also arise from a non-linear mode of action.

In addition, the non-cancer assessment for OPP established a chronic Reference Dose value of 39 mg/kg/day from the combined chronic toxicity/carcinogenicity study in rats (MRIDs 43954301, 44852701, 44832201) based on decreased body weight gains, decreased food consumption and reduced food efficiency, and increased clinical and gross pathological signs of toxicity at the LOAEL of 200 mg/kg/day. The selection of 39 mg/kg/day as the chronic RfD value is sufficiently protective of the key events involved in the carcinogenic mode of action, which are not present at doses below 200 mg/kg/day. Thus, the precursor events leading to development of bladder and liver tumors are not likely to occur using the selected chronic RfD value and this value is thus protective against development of tumors and, therefore, cancer is not an issue.

## 6.0 FQPA CONSIDERATIONS

### 6.1 Developmental Toxicity Study Conclusions

Developmental toxicity studies for OPP are available in both the rat and rabbit, as summarized in this toxicology chapter. Both studies were well conducted and considered acceptable by the Agency. The examination of these studies shows that adverse effects in offspring occurred at doses higher than those producing maternal toxicity. In addition, the effects on offspring were not considered more severe than those occurring in maternal animals. Therefore, there is no

increased concern for developmental toxicity of OPP when comparing effects in adult animals with those in offspring. This conclusion is similar to that reached by the Department for Environment, Food and Rural Affairs of the Pesticides Safety Directorate in their 1993 publication on the Evaluation of 2-phenyl phenol.

### 6.2 Reproductive Toxicity Study Conclusions

An acceptable two-generation reproduction toxicity study conducted according to Agency guidelines is available for OPP. There were no toxicologically significant effects on reproductive parameters in this study. Therefore, there is no increased concern for potential reproductive toxicity of OPP.

### 6.3 Information from Literature Sources

Peer reviewed scientific literature is available on both the reproductive and developmental toxicity of OPP (IPCS, 1999). None of these studies indicates increased concern for developmental or reproductive toxicity of OPP.

### 6.4 Pre-and/or Postnatal Toxicity

A. Determination of Susceptibility

From the available data submitted to the Agency and the available peer reviewed scientific literature on developmental and reproductive toxicity, there was no increased concern for susceptibility from exposure to OPP.

B. Degree of Concern Analysis and Residual Uncertainties

There are no residual uncertainties identified from examination of the available data on developmental and reproductive toxicity of OPP. Available submitted studies are well-conducted and identify clear dose-response relationships for parental and offspring toxicity. Peer reviewed literature supports the findings of the submitted studies.

C. Proposed Hazard-based Special FQPA Safety Factor(s):

The special hazard-based FQPA safety factor can be reduced to 1x for OPP.

### 6.5 Recommendation for a Developmental Neurotoxicity Study

There is no need for a developmental neurotoxicity study with OPP at this time. The available data show no significant neurotoxic effects from administration of the chemical in experimental animal studies.

## 7.0 SUMMARY OF TOXICOLOGICAL DOSES AND ENDPOINTS FOR O-PHENYLPHENOL FOR USE IN HUMAN RISK ASSESSMENT

### 7.1 Summary Table of Toxicological Dose and Endpoint Selection (Table 2)

**Table 2 Summary of Toxicological Doses and Endpoints for OPP for Use in Human Risk Assessments**

| Exposure Scenario | Dose Used in Risk Assessment (mg/kg/day) | Target MOE, UF, Special FQPA SF, for Risk Assessment | Study and Toxicological Effects |
|---|---|---|---|
| **Dietary Risk Assessments** | | | |
| **Acute Dietary** (general population and females 13-49) | No appropriate endpoints were identified that represent a single dose effect. Therefore, this risk assessment is not required. | | |
| **Chronic Dietary** (all populations) | **NOAEL** = 39 mg/kg/day | **FQPA SF** = 1<br>**UF** = 100 (10x inter-species extrapolation, 10x intra-species variation)<br><br>**Chronic RfD (cPAD)** = 0.39 mg/kg/day | Combined oral toxicity/carcinogenicity study in rats (MRID 43954301, 44852701, 44832201)<br><br>LOAEL of 200 mg/kg/day based upon decreased body weight, body weight gain, food consumption and food efficiency, increased clinical and gross pathological signs of toxicity. |
| **Non-Dietary Risk Assessments** | | | |
| **Incidental Oral** Short-Term (1 - 30 days) | **NOAEL (maternal)** = 100 mg/kg/day | **Target MOE** = 100 (10x inter-species extrapolation, 10x intra-species variation)<br>**FQPA SF** = 1 | Developmental (gavage) toxicity studies in rats (MRID 00067616, 92154037) and rabbits (MRID 41925003; co-critical developmental toxicity study)<br><br>Maternal LOAEL of 300 mg/kg/day based upon clinical observations of toxicity, decreased weight gain, food consumption and food efficiency observed in the rat developmental toxicity study. |
| | | | |

| Table 2 Summary of Toxicological Doses and Endpoints for OPP for Use in Human Risk Assessments | | | |
|---|---|---|---|
| Exposure Scenario | Dose Used in Risk Assessment (mg/kg/day) | Target MOE, UF, Special FQPA SF, for Risk Assessment | Study and Toxicological Effects |
| **Incidental Oral** Intermediate-Term (1 - 6 months) | **NOAEL** = 39 mg/kg/day | **Target MOE** = 100 (10x inter-species extrapolation, 10x intra-species variation) **FQPA SF** = 1 | Combined oral toxicity/carcinogenicity study in rats (MRID 43954301, 44852701, 44832201) LOAEL of 200 mg/kg/day based upon decreased body weight, body weight gain, food consumption and food efficiency, increased clinical and gross pathological signs of toxicity. |
| **Dermal** Short-Term (1 - 30 days) (residential and occupational) | **NOAEL (dermal)** = 100 mg/kg/day | **Target MOE** = 100 (10x inter-species extrapolation, 10x intra-species variation) | 21-Day Dermal toxicity study in rats (MRID 42881901) LOAEL (dermal) of 500 mg/kg/day based upon dermal irritation (erythema, scaling) at the site of test substance application. |
| **Dermal** Intermediate- and Long-Term (1 - 6 months and >6 months) (residential and occupational) | **NOAEL** = 39 mg/kg/day[a] | **Target MOE** = 100 (10x inter-species extrapolation, 10x intra-species variation) | Combined oral toxicity/carcinogenicity study in rats (MRID 43954301, 44852701, 44832201) LOAEL of 200 mg/kg/day based upon decreased body weight, body weight gain, food consumption and food efficiency (effects observed as early as 13 weeks in this study), increased clinical and gross pathological signs of toxicity. |
| **Inhalation** Short-Term (1 - 30 days) (residential and occupational) | **NOAEL (maternal)** = 100 mg/kg/day[b] | **Target MOE** = 100 (10x inter-species extrapolation, 10x intra-species variation) . An additional 10x factor for route-to-route extrapolation is used to determine the need for an inhalation toxicity study | Developmental (gavage) toxicity studies in rats (MRID 00067616, 92154037) and rabbits (MRID 41925003; co-critical developmental toxicity study) Maternal LOAEL of 300 mg/kg/day based upon clinical observations of toxicity, decreased weight gain, food consumption and food efficiency observed in the rat developmental toxicity study. |
| | | | |

| Table 2 Summary of Toxicological Doses and Endpoints for OPP for Use in Human Risk Assessments | | | |
|---|---|---|---|
| Exposure Scenario | Dose Used in Risk Assessment (mg/kg/day) | Target MOE, UF, Special FQPA SF, for Risk Assessment | Study and Toxicological Effects |
| **Inhalation** Intermediate- and Long-Term (1 - 6 months and >6 months)<br><br>(residential and occupational) | **NOAEL** = 39 mg/kg/day[b] | **Target MOE** = 100 (10x inter-species extrapolation, 10x intra-species variation)<br><br>An additional 10x factor for route-to-route extrapolation is used to determine the need for an inhalation toxicity study. | Combined oral toxicity/carcinogenicity study in rats (MRID 43954301, 44852701, 44832201)<br><br>LOAEL of 200 mg/kg/day based upon decreased body weight, body weight gain, food consumption and food efficiency (effects observed as early as 13 weeks in this study), increased clinical and gross pathological signs of toxicity. |
| **Cancer** | **Classification:** *OPP* is classified as "Not likely to be carcinogenic below a specific dose range." Quantitation of cancer risk is not required. | | |

UF = uncertainty factor, DB UF = data base uncertainty factor, FQPA SF = special FQPA safety factor, NOAEL = no observed adverse effect level, LOAEL = lowest observed adverse effect level, PAD = population adjusted dose (a = acute, c = chronic), RfD = reference dose, MOE = margin of exposure

[a] A default dermal absorption factor of 100% is used because an oral endpoint was selected for the intermediate- and long-term dermal exposure scenarios and there are no acceptable dermal absorption studies in animals available.

[b] The inhalation absorption factor of 100% (default value, assuming oral and inhalation absorption are equivalent) should be used since an oral endpoint was selected for the inhalation exposure scenarios.

## 8.0 TOXICITY PROFILE TABLES

### 8.1 Acute Toxicity Profile Table - (See Section 4.1, Acute Toxicity, Table 1).

### 8.2 Subchronic, Chronic and Other Toxicity Profiles Table (Table 3)

| Table 3: Subchroninc, Chronic, and other Toxicity Profiles for OPP and its Sodium salt. | | |
|---|---|---|
| **Guideline Number/ Study Type/ Test Substance (% a.i.)** | **MRID Number (Year)/ Citation/ Classification/ Doses** | **Results** |
| 870.3100<br>Subchronic oral - Rats<br>OPP purity > 98% | MRID 40760206<br>Iguchi, et al. (1984)<br>Acceptable - Guideline<br>0, 0.156, 0.313, 0.625, 1.25, or 2.5%<br>(0, 182, 391, 761, 1669, or 2798 mg/kg/day (males)<br>0, 202, 411, 803, 1650, or 3014 mg/kg/day (females)) | Subchronic Toxicity:<br>NOAEL = 761 mg/kg/day (males)<br>= 803 mg/kg/day (females)<br>LOAEL = 1669 mg/kg/day (males)<br>= 1650 mg/kg/day (females)<br>Based on significant reductions in body weight gain and food and water consumption.<br><br>Mortality occurred at the high dose groups within 2 weeks of study initiation in 20% of the males and 10% of females. Food consumption was slightly decreased in males and females of the two high doses. Water consumption was significantly decreased from controls in the first week of the study in the two high dose groups. The hemoglobin (Hgb) and mean red blood corpuscle hemoglobin concentration (MCHC) were significantly lower at the two high doses in females and in males at the high dose. No treatment-related effects were observed in the serum analyses. Pathological and histological observations indicated treatment-related inflammation of the kidneys in both males and females and abnormal growth in the mucous membrane of the male bladder (most pronounced in the 1.25%, 1669 and 1650 mg/kg/day, dose groups). |
| 870.3200<br>21-day dermal - Rat<br>OPP purity 99.82% | MRID 42881901<br>Zempel and Szabo (1993)<br>Acceptable - Guideline<br>0, 100, 500, or 1000 mg/kg/day, 6 hours per day, 15 doses | Dermal Toxicity:<br>NOAEL = 100 mg /kg/day<br>LOAEL = 500 mg /kg/day, based on increased incidence of dermal irritation<br><br>Systemic Toxicity:<br>NOAEL ≥ 1000 mg/kg/day (highest dose tested)<br>LOAEL > 1000 mg/kg/day (not established)<br><br>Erythema, scaling, and an increased incidence of acanthosis and hyperkeratosis was observed in male and female rats at the 500 and 1000 mg/kg dose levels. From the data in this study, female rats appeared to be more sensitive. |

| Table 3: Subchroninc, Chronic, and other Toxicity Profiles for OPP and its Sodium salt. | | |
|---|---|---|
| **Guideline Number/ Study Type/ Test Substance (% a.i.)** | **MRID Number (Year)/ Citation/ Classification/ Doses** | **Results** |
| 870.3700<br>Developmental –Rat<br>OPP purity 99.69% | MRID 92154037 Reformat of 67616 and 164362<br>John, et al. (1978)<br>Acceptable - Guideline<br>0, 100, 300, or 700 mg/kg/day, GD 6 to 15 | Maternal Toxicity:<br>NOAEL = 100 mg/kg/day<br>LOAEL = 300 mg/kg/day, based on decreased body weight gains, food consumption, and food efficiency.<br><br>Developmental Toxicity:<br>NOAEL ≥ 700 mg/kg/day (highest dose tested)<br>LOAEL > 700 mg/kg/day (not established)<br><br>Decreased body weight gain was observed at the mid (91% of control) and high-dose (79% of control) groups. Food consumption and food efficiency were slightly reduced in the mid and high-dose groups. Also, the high-dose group had reduced liver weights. |
| 870.3700<br>Developmental –Rabbit<br>OPP purity 99.88% | MRIDs 41925001 (range-finding), 41925002 (pilot), and 41925003 (developmental)<br>Zablotney, et al. (1991)<br>Acceptable - Guideline<br>0, 25, 100, or 250 mg/kg/day, GD 7 to 19 | Maternal toxicity<br>NOAEL = 100 mg/kg/day<br>LOAEL = 250 mg/kg/day, based on increased incidence of mortality and renal inflammation/tubular degeneration.<br><br>Developmental toxicity<br>NOAEL ≥ 250 mg/kg/day (highest dose tested)<br>LOAEL > 250 mg/kg/day (not established)<br><br>At the highest dose tested, an increase in mortality (three dams compared to one dam in the control group) and treatment-related alterations in microscopic kidney structure, primarily consisting of inflammation and tubular degeneration, were noted. Although observations of blood in the feces, urine, or cage pan was noted in the mid-dose (three dams compared to one control dam) and high-dose (6 dams compared to one control dam) groups, these effects were determined to be of no toxicological significance because there was no correlation of these effects with signs of abortion and/or gross/microscopic pathologies. |

| Table 3: Subchroninc, Chronic, and other Toxicity Profiles for OPP and its Sodium salt. | | |
|---|---|---|
| **Guideline Number/ Study Type/ Test Substance (% a.i.)** | **MRID Number (Year)/ Citation/ Classification/ Doses** | **Results** |
| 870.3800<br>Reproduction – Rat<br>OPP purity >99% | MRIDs 43928801<br>Acceptable - Guideline<br>0, 20, 100, or 500 mg/kg/day | Maternal toxicity<br>NOAEL = 100 mg/kg/day<br>LOAEL = 500 mg/kg/day, based on increased reduced body weight and body weight gain in adults, reduced body weight in 21-day old pups, clinical signs in adult male rats, microscopic lesions in the kidneys, and gross microscopic lesions in the urinary bladder of adult male rats, and the death of one adult male rat due to kidney failure.<br><br>Reproductive Toxicity:<br>NOAEL ≥ 500 mg/kg/day (highest dose tested)<br>LOAEL > 500 mg/kg/day (not established) |
| 870.4300<br>Combined chronic toxicity/ Carcinogenicity – Rat<br>OPP purity 99.5 - 100% | MRID 43954301, supplemental submissions MRID 448322701 and 44852701<br>Wahle and Christenson (1996)<br>Acceptable - Guideline<br>0, 800, 4000, or 8000 ppm (males) (0, 39, 200, or 402 mg/kg/day)<br>0, 800, 4000, or 10,000 ppm (females) (0, 49, 248, or 647 mg/kg/day) | Systemic Toxicity:<br>NOAEL = 800 ppm<br>= 39 mg/kg/day (males)<br>= 49 mg/kg/day (females)<br>LOAEL = 4000 ppm<br>= 200 mg/kg/day (males)<br>= 248 mg/kg/day (females)<br>Based on decreased body weight gains, food consumption and food efficiency, and increased clinical and gross pathological signs of toxicity. |
| 870.4200<br>Carcinogenicity – Mouse<br>OPP purity 99.88% | MRID 43545501<br>Quast and McGuirk (1995)<br>Acceptable - Guideline<br>0, 250, 500, or 1000 mg/kg/day) | Systemic Toxicity:<br>NOAEL < 250 mg/kg/day<br>LOAEL = 250 mg/kg/day<br>Based on increased liver and reduced spleen weights and gross observations in the liver of all treated animals. |

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